REMARKS

Claims 1-28 were pending in this application. According to the May 21, 2002 Office Action, claims 7-12 were withdrawn from consideration and claims 1-6 and 13-28 were rejected. Applicant has amended claims 6, 13 and 17. Accordingly, claims 1-28 are under consideration. Applicant maintains that the amendments do not introduce any new matter.

Rejection under 35 U.S.C. §112

The Examiner rejected claims 3, 6 and 13-19 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In response, Applicant respectfully traverses the rejection of claim 3. The term "androgenic agent" clearly refers to any compound that acts as an androgen with regard to its biological activity. The term "androgen" is well defined in the art as a male sex hormone (see attached page 84 of Webster's Ninth Collegiate Dictionary). Accordingly, the Examiner is kindly requested to withdraw this rejection.

With regard to the expression "R100" in claim 13, Applicant has amended claim 13 to give a more precise definition of this expression. Furthermore, Applicant has amended claims 6 and 17 to delete the trade names of SERMs as suggested by the Examiner. Accordingly, the Examiner is kindly requested to withdraw this rejection.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 1-6 and 13-28 under 35 U.S.C. §103 as allegedly unpatentable over Labrie '720, Labrie '107, and Labrie et al. '201.

In response, Applicant respectfully traverses the Examiner's rejection. Labrie '720 teaches only that androgenic compounds are useful in the treatment and prevention of breast and endometrial cancers or bone loss. Contrary to the Examiner's affirmation, it does not teach that 17β-estradiol is used in estrogen therapy in menopausal women.

The Examiner has misunderstood the subject of Labrie '107 which does not teach that 17β-estradiol is capable of inhibiting breast tumor or cancer growth. One skilled in the art knows that, contrary to the Examiner's affirmation, 17β-estradiol increases the growth of most of the breast tumors. The subject of this reference is the treatment of breast and endometrial cancer with a combination of an antiestrogen and a compound selected from the group consisting of an androgen, a progestin and an inhibitor of sex steroid formation. Moreover, DHEA is never mentioned as a drug in this reference.

Labrie '201 discloses compounds such as EM-652 and its pharmaceutical acceptable salts having anti-estrogen activities and being useful in methods of treating estrogen-sensitive or -dependent diseases such as breast cancer.

It is page 2, lines 3-4 of the specification of the present application that discloses that the administration of estrogens is useful in the treatment of menopausal symptoms. The Examiner admits that the combination of an estrogen and the particular SERM, EM-652.HCl, or further combined with DHEA is not expressly disclosed in the prior art. However, the Examiner's argument demonstrating the obviousness of the present invention is erroneous because it is based on the wrong assumption that the prior art discloses that 17β-estradiol is capable of inhibiting breast tumor or cancer growth.

Thus, the cited references cannot render obvious the combination of EM-652.HCl and an estrogen for reducing or eliminating the incidence of menopausal symptoms.

The present invention teaches a combination of EM-652.HCl and an estrogen. The reasons for which this combination is better than a SERM alone, or estrogens alone, are clearly explained for each disease (menopause, hot flashes, sweats, breast tenderness, vaginal bleeding) in the specification from page 9, line 13 to page 10, line 12: "The estrogen replacement therapy is commonly ... reduction of hot flashes and sweats." The Examiner's attention is also drawn to page 20, line 12 to page 21, line 25: "Preferred SERMs have side chains ... from Fig. 10."

Thus, the essence of the present invention is that SERMs reverse the negative effects of estradiol without diminishing its positive effects, each effect or site of action being tissue-

specific. In particular, the Examiner's attention is drawn to the unexpected results in Example 9 demonstrating that compounds of the EM-652.HCl family cannot pass through the brain barrier. Explanations and consequences are given on page 22, line 21 to page 23, line 6, for hot flashes, cardiovascular symptoms, Alzheimer's disease, loss of cognitive functions and insomnia.

For "Hot flashes ... conditions," the present specification teaches that: "they (compounds of EM-652.HCl family) cannot antagonize the positive effect of estrogens in brain but they antagonize the negative effects of estrogens in the breast, uterine, and endometrial tissues ...." See also page 23, lines 7-18: "The overall additive benefits of combining an estrogen and a SERM" ... ovariectomy on bone mineral density."

Furthermore, concerning the further addition of DHEA, none of the references cited by the Examiner mentions the action of DHEA as a drug.

Accordingly, the present application demonstrates the unexpected advantages of combining SERMs with estrogens as indicated above. The cited prior art references either alone or in combination do not teach or suggest the present invention and thus the Examiner is kindly requested to withdraw this rejection.

In light of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited. If there are any issues or amendments the Examiner wishes to discuss, the Examiner is encouraged to contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on August 20, 2002:

Charles C. Achkar
Name of applicant, assignee or Registered Representative

Charles Achkar
Signature

August 20, 2002
Date of Signature

WOG/CCA:lac

Respectfully submitted,

Charles Achkar

Charles C. Achkar
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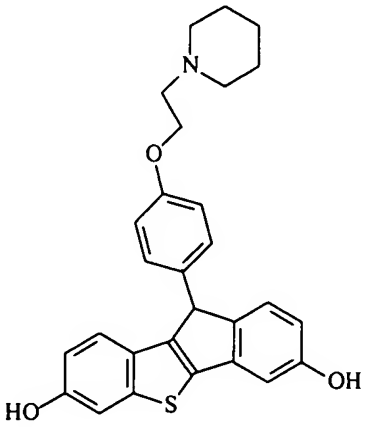
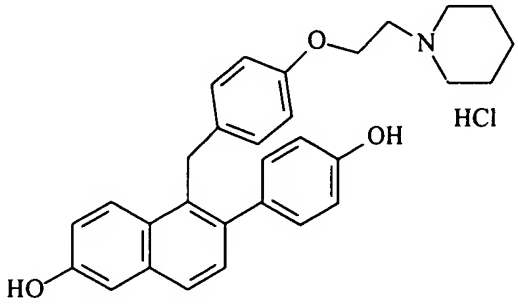
APPENDIX A
"Clean" Version of Each Paragraph/Section/Claim
37 C.F.R. § 1.121(b)(ii) and (c)(i)

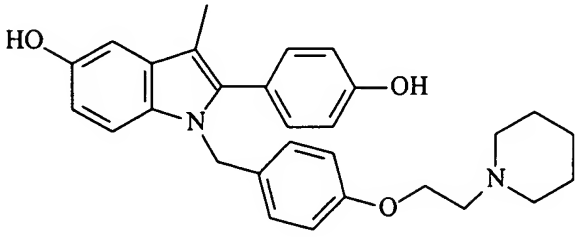
CLAIMS (with indication of amended or new):

(Amended) 6. The method of claim 4, wherein the selective estrogen receptor modulator is selected from the group consisting of a triphenylethylene derivative, benzopyran derivative,



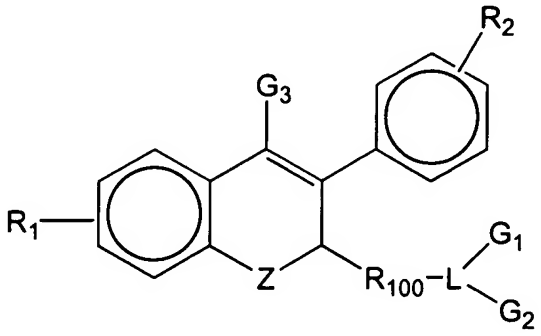


and



and centchroman derivative.

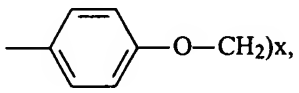
(Amended) 13. The method of claim 4 wherein the selective estrogen receptor modulator has the following formula:



wherein R_1 and R_2 are independently hydrogen, hydroxyl or a moiety which is converted to hydroxyl in vivo;

wherein Z is either absent or selected from the group consisting of $-CH_2-$,-0-,-S- and $-NR_3-$ (R_3 being hydrogen or lower alkyl);

wherein R100 is



x being an integer from 1 to 5;

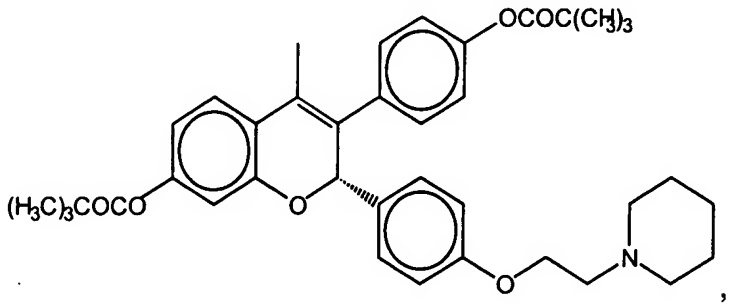
wherein L is a bivalent or trivalent moiety selected from the group of -SO-, -CON-, -N<, and -SON< ;

wherein G_1 is selected from the group consisting of hydrogen, a C_1 to C_5 hydrocarbon, a bivalent moiety which in combination with G_2 and L is a 5-to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

wherein G_2 is either absent or selected from the group consisting of hydrogen, a C_1 to C_5 hydrocarbon, a bivalent moiety which in combination with G_1 and L is a 5-to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

wherein G_3 is selected from the group consisting of hydrogen, methyl and ethyl.

(Amended) 17. The method of claim 15, wherein said selective estrogen receptor modulator is selected from the group consisting of:



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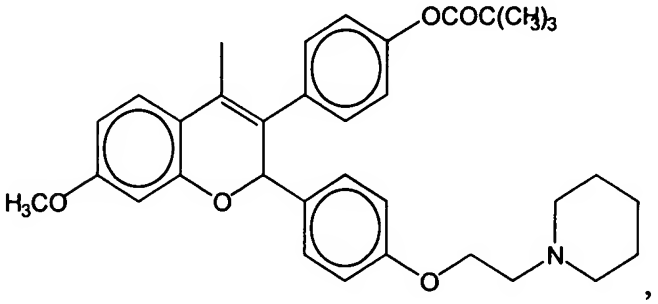

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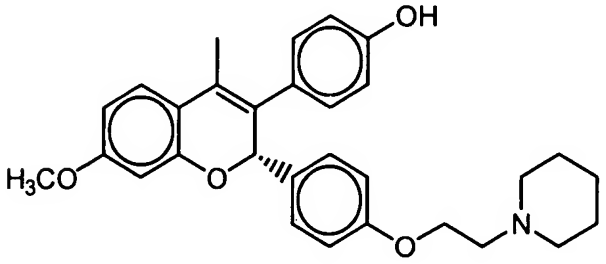

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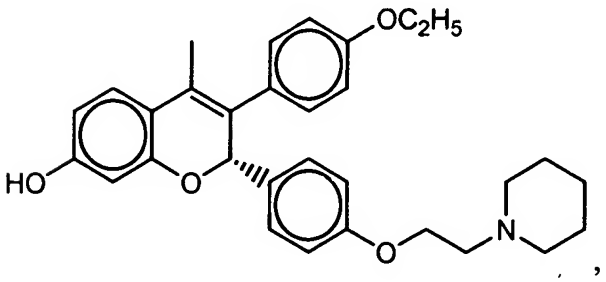

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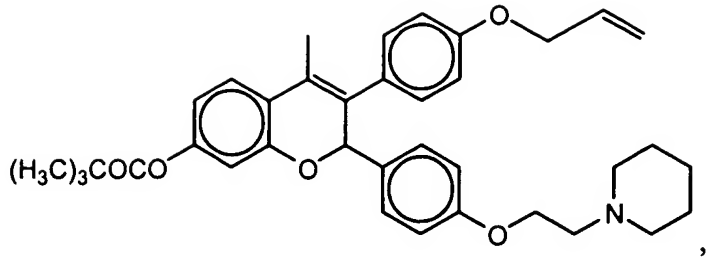
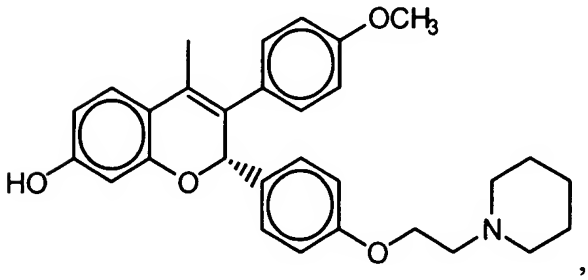
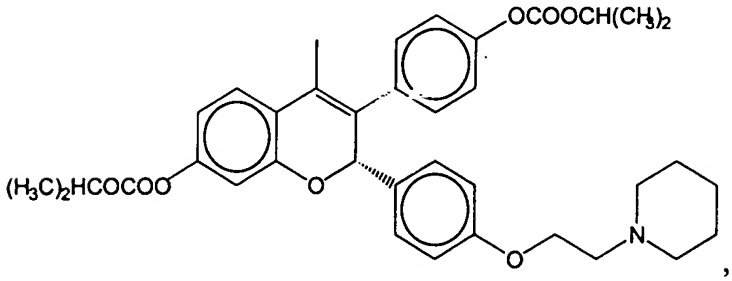
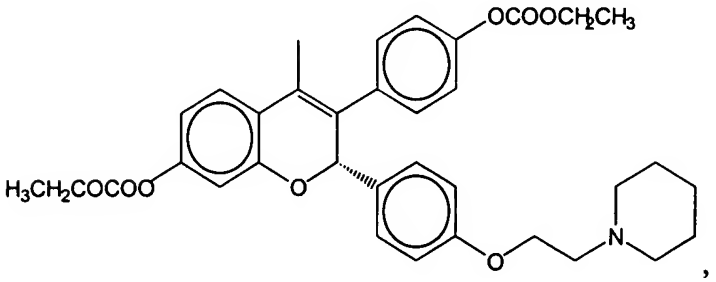
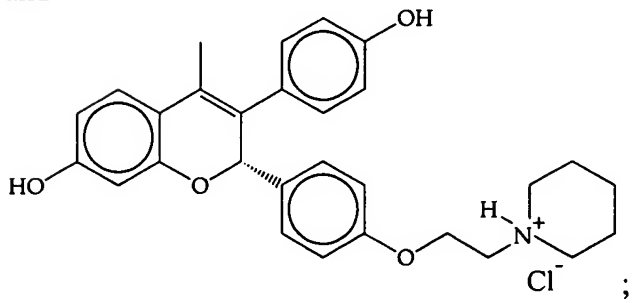

(H3C)3COCO
O
O
N
,


OCH3
HO
O
O
N
,


OCOOCH(CH3)2
(H3C)2HCOCOO
O
O
N
,


OCOOCH2CH3
H3CH2COCOO
O
O
N
,

and

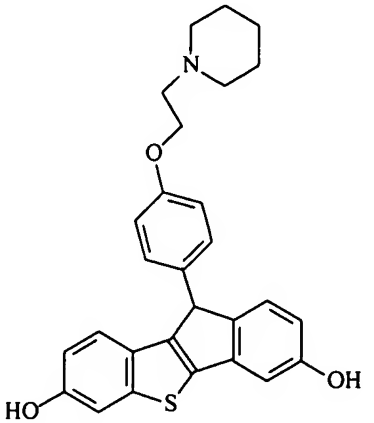

OH
HO
O
H
N+
O
Cl-
;

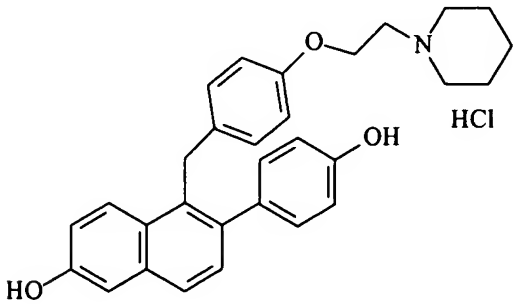
wherein all of the foregoing molecular structures whose stereochemistry is indicated are optically active due to a majority of their stereoisomers being of 2S configuration.

APPENDIX B
Version with Markings to Show Changes Made
37 C.F.R. § 1.121(b)(iii) and (c)(ii)

CLAIMS:

6. The method of claim 4, wherein the selective estrogen receptor modulator is selected from the group consisting of a triphenylethylene derivative, benzopyran derivative, [HMR 3339, HMR 3656, LY 335124, LY 326315, SH 646, ERA 923]





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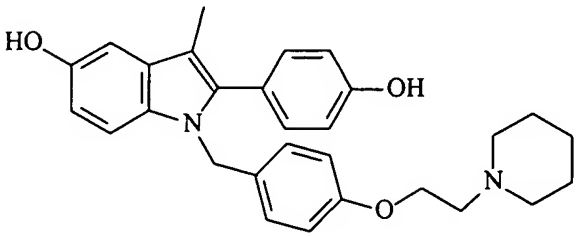
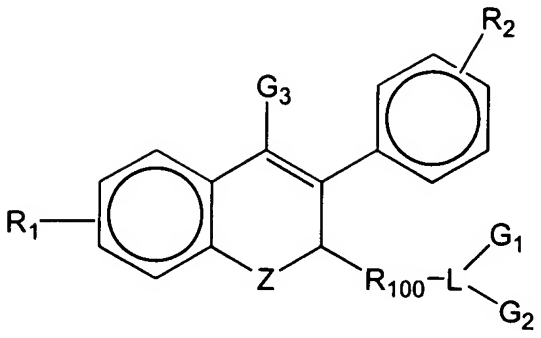


and centchroman derivative.

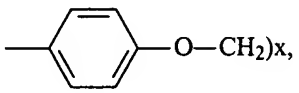
13. The method of claim 4 wherein the selective estrogen receptor modulator has the following formula:



wherein R_1 and R_2 are independently hydrogen, hydroxyl or a moiety which is converted to hydroxyl in vivo;

wherein Z is either absent or selected from the group consisting of $-CH_2-$,-0-,-S- and $-NR_3-$ (R_3 being hydrogen or lower alkyl);

wherein [the]R100 is [a bivalent moiety which distances L from the B-ring by 4-10 intervening atoms]



x being an integer from 1 to 5;

wherein L is a bivalent or trivalent moiety selected from the group of -SO-, -CON-, -N<, and -SON< ;

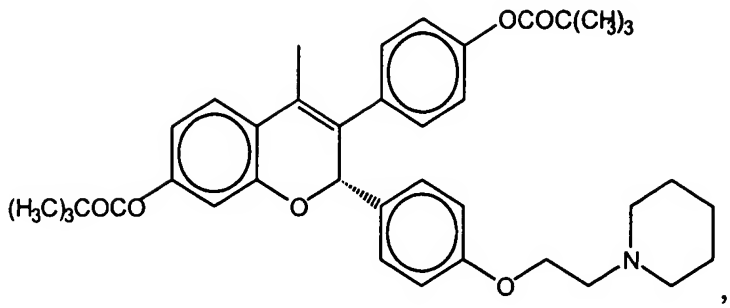
wherein G_1 is selected from the group consisting of hydrogen, a C_1 to C_5 hydrocarbon, a bivalent moiety which in combination with G_2 and L is a 5-to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

wherein G_2 is either absent or selected from the group consisting of hydrogen, a C_1 to C_5 hydrocarbon, a bivalent moiety which in combination with G_1 and L is a 5-to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

wherein G_3 is selected from the group consisting of hydrogen, methyl and ethyl.

17. The method of claim 15, wherein said selective estrogen receptor modulator is selected from the group consisting of:

[EM-800]



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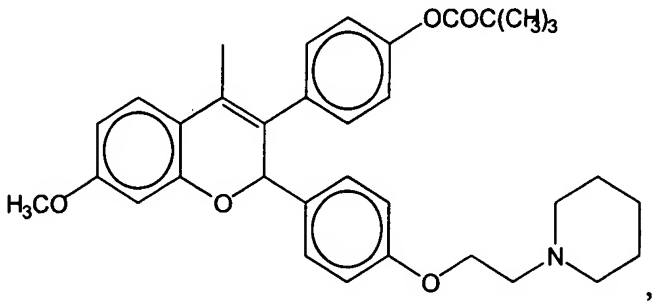
[EM-1520]



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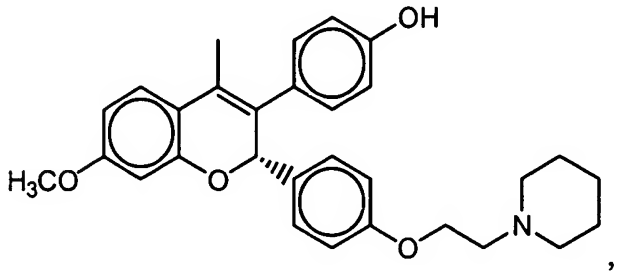
[EM-1872]



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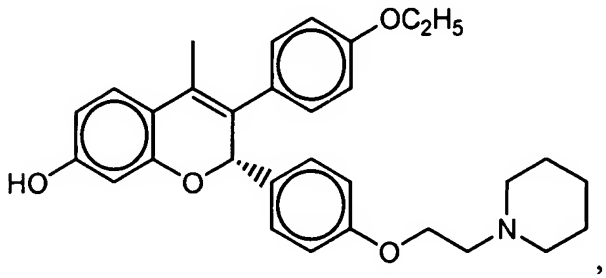
[EM-1900]



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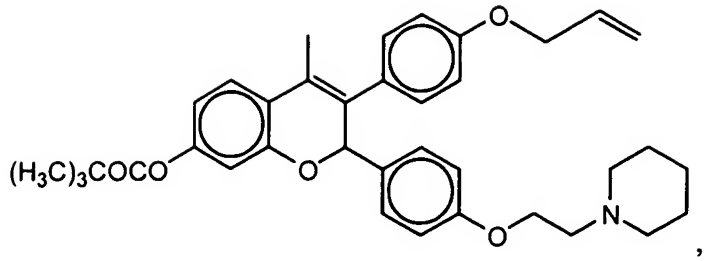
[EM-1901]



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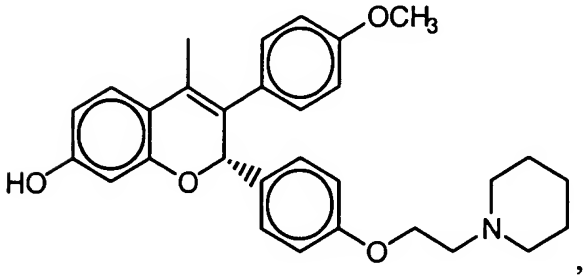
[EM-1903]



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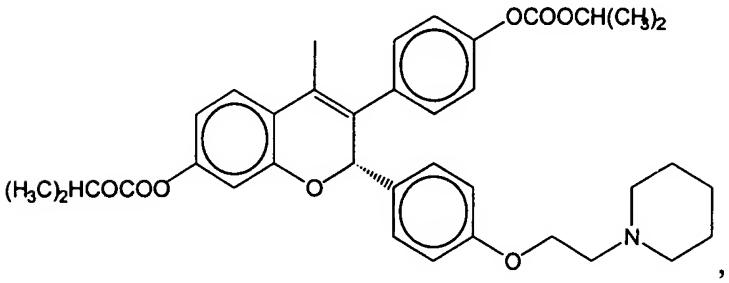
[EM-1533]



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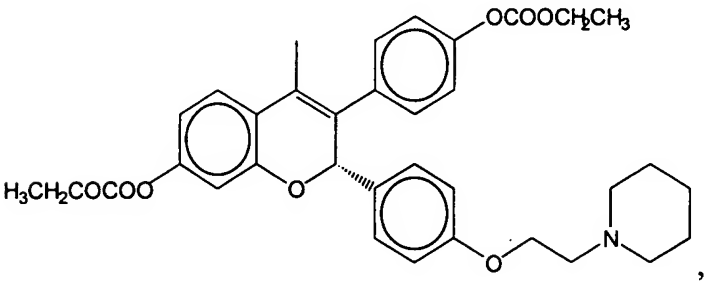
[EM-1518]



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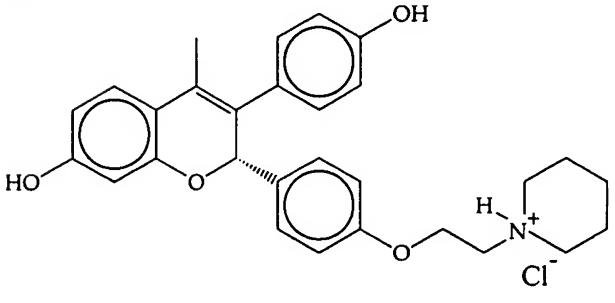
and

[EM-652.HCl (EM-1538)]



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wherein all of the foregoing molecular structures whose stereochemistry is indicated are optically active due to a majority of their stereoisomers being of 2S configuration.